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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification [7] :
C07D 243/14, C07C 225/12, 237/06

A1

(11) International Publication Number: **WO 00/63186**

(43) International Publication Date: 26 October 2000 (26.10.00)

(21) International Application Number: PCT/EP00/03260

(22) International Filing Date: 12 April 2000 (12.04.00)

(30) Priority Data:
9908662.1 15 April 1999 (15.04.99) GB

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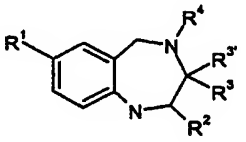
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PROCESS AND INTERMEDIATES FOR PREPARING BENZODIAZEPINES



(I)

(57) Abstract

A new process and intermediates for preparing 1,4–benzodiazepines of formula (I) is disclosed: wherein, R^1 is H, OH, Br, I, NR^5R^6, CO_2R^7, CF_3SO_3, C_{1-4}alkoxy, or (4,4'–bipiperidinyl) carbonyl; R^2 is alkyl, optionally substituted by CO_2R^7 or $CONR^5R^6$; R^3 and $R^{3'}$ are independently H, Ar or C_{1-6} alkyl optionally substituted by OH, NO_2, NH_2, NR^5R^6, halogen, CO_2R^7, $CONR^5R^6$ or Ar, or together R^3 and $R^{3'}$ are =O; R^4 is H or C_{1-4} alkyl, optionally substituted by OH, NO_2, NH_2, NR^5R^6, halogen, CO_2R^7, $CONR^5R^6$, or Ar; R^5 and R^6 are independently H, Ar, C_{1-6}alkyl, HCO, C_{1-6}alkyl–CO, Ar–CO, C_{1-6}alkyl–SO_2, or Ar–SO_2; and R^7 is a carboxylic acid protecting group.

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PROCESS AND INTERMEDIATES FOR PREPARING BENZODIAZEPINES

Field of the Invention

This invention relates to processes and intermediates for preparing benzodiazepine vitronectin and fibrinogen antagonists.

Background

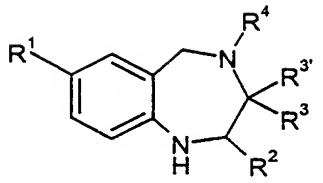
Tetrahydro-1,4-benzodiazepines form the core structure of a variety of pharmaceutically useful compounds. In particular, WO 93/00095 (PCT/US92/05463), WO 94/14776 (PCT/US93/12436), and WO 95/18619 (PCT/US95/00248) disclose 7-substituted tetrahydro-1,4-benzodiazepines which are reported to be inhibitors of the fibrinogen and vitronectin receptors and are useful as inhibitors of platelet aggregation, osteoporosis, angiogenesis and cancer metastasis. These publications contain a variety of procedures for constructing the basic 1,4-benzodiazepine structure. The prior processes employ expensive reagents and generally require a large number of synthetic steps in the sequence.

We have now discovered new useful intermediates and a new process for preparing certain 7-substituted 1,4-benzodiazepines. The new process uses a unique cyclization step to form the diazepine ring, and is adaptable to a large scale.

Teuber et al., Chem. Ber., 98, 2648 (1965), have reported an oxidative method for forming an indole, and Kraus et al., Tet. Lett., 39, 3957 (1998), have reported a cyclization for forming a 3,4-dihydro-1,4-benzodiazepine-2,5-dione, using an acyl hydroquinone and Fremy's salt. Kraus et al., Tet. Lett., 40, 2039 (1999), have also reported using Fremy's salt to promote an unusual rearrangement of a 1,4-benzodiazepine-5-one, presumably through a 1-acyl quinone. The compounds of the instant invention do not possess the stabilizing acyl hydroquinone arrangement found in these compounds.

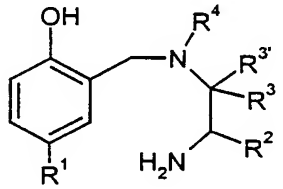
Summary of the Invention

In one aspect this invention is a new process for preparing 1,4-benzodiazepines of formula (I):



(I)

wherein R^1-R^7 are as defined hereinafter, from substitued 2-hydroxy phenols of formula (II):



(II)

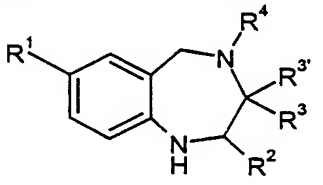
which comprises reacting a compound of the formula (II) with an oxidizing agent wherein R and R^1-R^7 are as defined hereinafter.

In another aspect this invention comprises new compounds for preparing 1,4-benzodiazepines.

In yet another aspect this process may be used to prepare 2,3,4,5-tetrahydro-7-(4,4'-bipiperidinylcarbonyl)-3-oxo-4-methyl-1H-1,4-benzodiazepine-2-acetic acid, and related active pharmaceutical agents.

Detailed Description of the Invention

Many compounds that are useful as pharmaceuticals or intermediates for preparing pharmaceuticals are given by formula (I):



(I)

wherein,

R^1 is H, OH, Br, I, NR^5R^6, CO_2R^7, CF_3SO_3, C_{1-4}alkoxy, or (4,4'-bipiperidinyl)carbonyl;

R^2 is alkyl, optionally substituted by CO_2R^7 or $CONR^5R^6$;

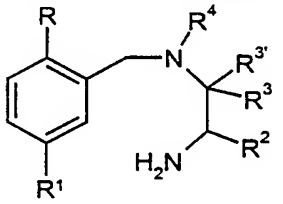
R^3 and $R^{3'}$ are independently H, Ar or C_{1-6}alkyl optionally substituted by OH, NO_2, NH_2, NR^5R^6, halogen, CO_2R^7, $CONR^5R^6$or Ar, or together R^3 and $R^{3'}$ are =O;

R^4 is H or C_{1-4} alkyl, optionally substituted by OH, NO_2, NH_2, NR^5R^6, halogen, CO_2R^7, $CONR^5R^6$, or Ar;

R^5 and R^6 are independently H, Ar, C_{1-6}alkyl, HCO, C_{1-6}alkyl-CO, Ar-CO, C_{1-6}alkyl-SO_2, or Ar-SO_2; and

R^7 is a carboxylic acid protecting group.

Compounds of formula (I) may be prepared by a process which comprises, reacting a compound of the formula (II) with an oxidizing agent,



(II)

wherein

R is OH or C_{1-4}alkoxy, and R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined above, and thereafter, treating with a reducing agent.

Preferably R is OH.

Preferably, R^1 is H, OH, NH_2, bromo, iodo, CO_2R^7, or C_{1-4}alkoxy. More preferably, R^1 is H or OH.

Preferably, R^2 is $CH_2CO_2R^7$ or $CH_2CONR^5R^6$; more preferably $CH_2CO_2R^7$.

Preferably, R^3 and $R^{3'}$ are =O.

Preferaby, R^4 is H, C_{1-4}alkyl or Ar-C_{1-4}alkyl. Methyl is especially preferred.

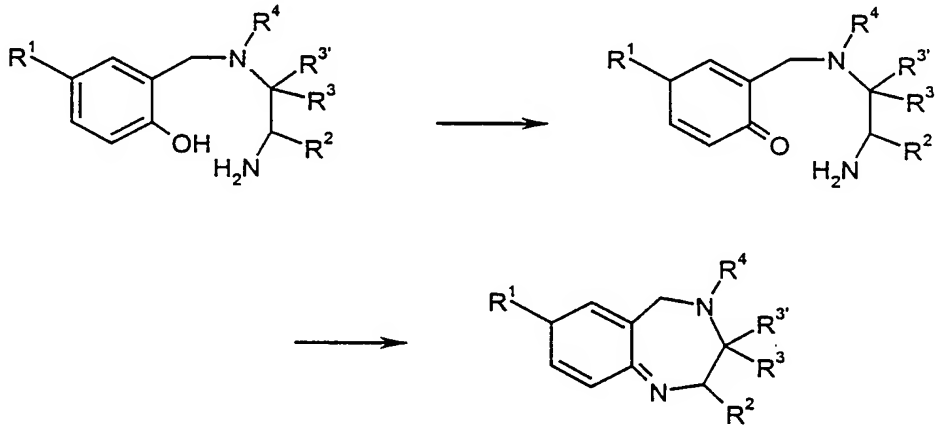
Preferably R^7 is C_{1-4}alkyl, phenyl or benzyl. Methyl, t-butyl or benzyl is especially preferred.

Suitably, R and R^1 are each OH or OCH_3. Most preferably, R and R^1 are OH.

Compounds of formula (II), wherein R, and R^1-R^4 are as defined above, are useful for the preparation of the compounds of formula (I) and are a feature of this invention. A preferred embodiment comprises compounds of formula (II) wherein R is OH or C_{1-4}alkoxy; R^1 is H, OH, Br, I, C_{1-4}alkoxy,CO_2R^7, CF_3SO_3, or (4,4'-bipiperidinyl)carbonyl, optionally protected on the basic nitrogen; R^4 is methyl, and R^7 is a carboxy protecting group.

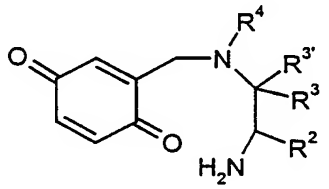
The condensation reaction to form the diazepine ring presumably proceeds through a Schiff's base-type intermediate, as illustrated in Scheme 1, so the oxidant used must be

Scheme 1



sufficient to promote oxidation of the aromatic hydroxyl group to a carbonyl and induce the free amino group to condense with it. Salts of ferricyanide and nitrosodisulfonate are useful, especially potassium ferricyanide and potassium nitrosodisulfonate. Agents of similar oxidation potential are also useful, such as silver (I) oxide, thallium (IV) nitrate, cerium (IV) ammonium nitrate, hypervalent iodine compounds, palladium on charcoal with a hydrogen acceptor (e.g., nitrobenzene), acid dichromate, lead tetra-acetate, and potassium periodate. Potassium nitrosodisulfonate (Fremy's salt) is a preferred reactant. Acetic acid and hydrochloric acid are preferred acids for use in the reaction, although other organic acids and mineral acids may also be suitable.

It will be apparent that when R^1 is a hydroxyl group, the reaction may proceed through a quinone-type intermediate, as indicated by the compounds of formula (III), wherein R^2, R^3 and R^4 are as defined in formula (I).



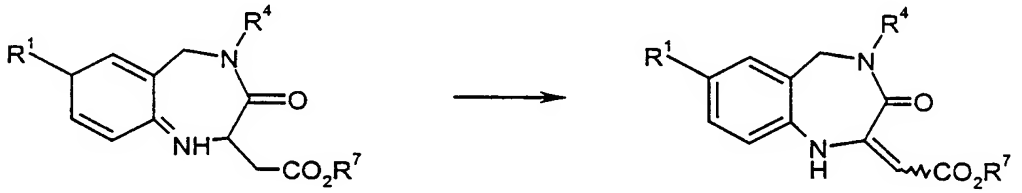
(III)

For instance, a preferred compound is (3*S*)-methyl 3-amino-4-(*N*-methyl-*N*-(1,4-benzoquinonylmethyl)carbamoyl) butanoate,

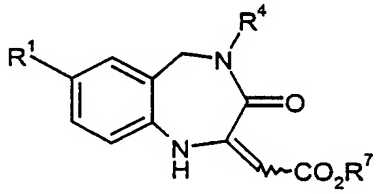
Reduction of the double bond completes the construction of the 2,3,4,5 tetrahydro-1,4-benzodiazepine ring system. Reduction may be accomplished readily by catalytic hydrogenation, such as by hydrogenation over palladium or platinum, although other means, such as transfer hydrogenation, for instance using ammonium formate and Pd/C in refluxing methanol, may be suitable.

In cases where further unsaturation is present in the ring system, tautomerisation of the Schiff's base may occur. For instance, when there is a 3-oxo group and a 2-acetic acid group, the double bond may tautomerize, as indicated in Scheme 2.

Scheme 2



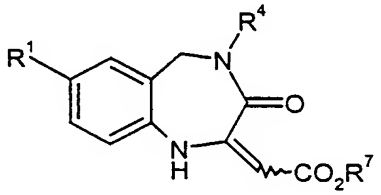
Thus, 1,4-benzodiazepine ring systems that have 3-oxo, 2-acetic acid substituents tautomerize to a 2-ethylidene configuration, and compounds of formula (IV):



(IV)

wherein R^1 is H, OH, Br, I, NR^5R^6, CO_2R^7, CF_3SO_3, C_{1-4}alkoxy, or (4,4'-bipiperidinyl)carbonyl; R^4 is H or C_{1-4} alkyl, optionally substituted by OH, NO_2, NH_2, NR^5R^6, halogen, CO_2R^7, $CONR^5R^6$, or Ar; R^5 and R^6 are independently H, Ar, C_{1-6}alkyl, HCO, C_{1-6}alkyl-CO, Ar-CO, C_{1-6}alkyl-SO_2, or Ar-SO_2; and R^7 is a carboxylic acid protecting group, are useful intermediates for preparing pharmaceutically active compounds, such as those disclosed in WO 95/18619 (PCT/US95/00248); WO 93/00095 (PCT/US/92/05463) and WO 94/14776 (PCT/US93/12436). Preferably R^1 is H or OH, and R^4 is methyl.

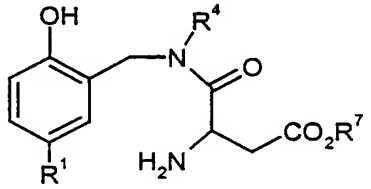
In a preferred embodiment, this invention is a process for preparing the active pharmaceutical product 2,3,4,5-tetrahydro-7-(4,4'-bipiperidinylcarbonyl)-3-oxo-4-methyl-1H-1,4-benzodiazepine-2-acetic acid, comprising reacting a compound of the formula (V):



(V)

wherein R^1 is H, OH, I, Br, CO_2R^7, CF_3SO_2, C_{1-4}alkoxy, or (4,4'-bipiperidinyl)carbonyl, optionally protected on one nitrogen; R^4 is methyl, and R^7 is a carboxy protecting group;with a reducing agent; and, if necessary, converting R^1 to (4,4'-bipiperidinyl)carbonyl, and, if necessary, removing any protecting groups. It will be apparent that the α,β unsaturated ester may be reduced at any point in the synthesis subsequent to the cyclization reaction. Reduction may be accomplished, for instance, using palladium or platinum on carbon. Preferably, R^1 is H or OH.

In a another preferred embodiment, this invention is a process for preparing 2,3,4,5-tetrahydro-7-(4,4'-bipiperidinylcarbonyl)-3-oxo-4-methyl-1H-1,4-benzodiazepine-2-acetic acid, comprising treating the compound of formula (VI):



(VI)

wherein R^1 is H, OH, I, Br, CO_2R^7, CF_3SO_3, C_{1-4}alkoxy, or (4,4'-bipiperidinyl)carbonyl, optionally protected on the basic nitrogen; R^4 is methyl; and R^7 is a carboxy protecting group;

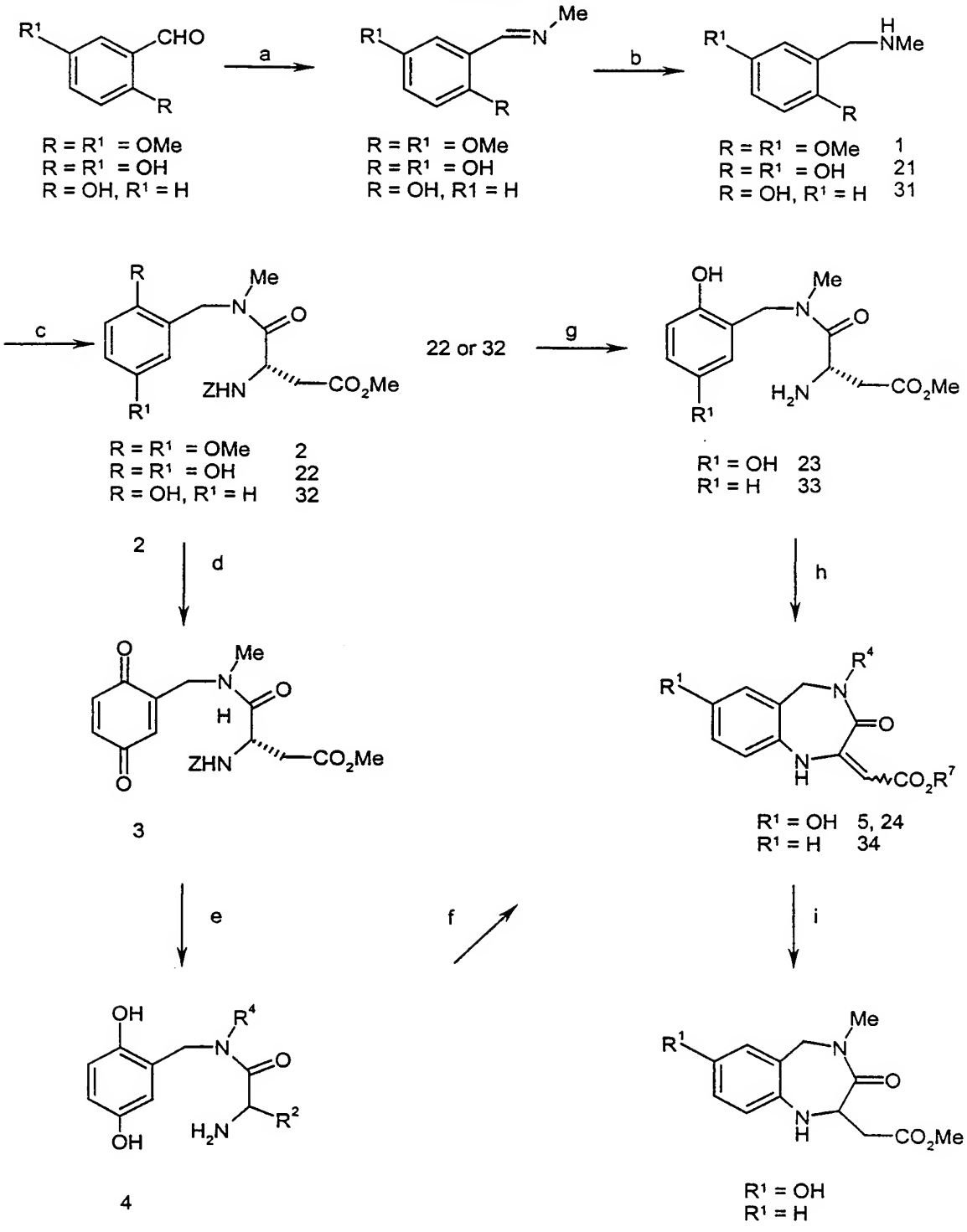
with an oxidizing agent, and, in any order, treating with a reducing agent and, if necessary, converting R^1 to (4,4'-bipiperidinyl)carbonyl; and, if necessary, removing any protecting groups. Preferably, R^1 is H or OH, and the product is converted to 2,3,4,5-tetrahydro-7-(4,4'-bipiperidinylcarbonyl)-3-oxo-4-methyl-1H-1,4-benzodiazepine-2-acetic acid via a palladium catalyzed aminocarbonylation.

It will be understood that one may use a variety of functional groups in the process for R^1, and subsequently transform such groups to the (4,4'-bipiperidinyl)carbonyl sidechain. For instance, one may convert a hydroxyl group at R^1 to a triflate group, and add the bipiperidinylcarbonyl group via a palladium catalyzed aminocarbonylation reaction, as described in WO 97/24336 (PCT/IB96/01502). It will of course be evident that an alkoxy substituent may be converted to a hydroxy substituent, such as by hydrolysis, and further transformed by similar means to the desired 4,4'-bipiperidinylcarbonyl group. One may also use an aminocarbonylation reaction to convert the bromo or iodo group to the bipiperidinylcarbonyl amino group. Additionally, a hydrogen at R^1 may be converted to bromo or iodo group, as described for instance in WO 97/24336 (PCT/IB96/01502), and converted via an aminocarbonylation reaction to the bipiperidinylcarbonyl group. An ester group may be hydrolyzed to a carboxyl group and reacted with the bipiperidinyl group using conventional amide bond forming reagents, such as dicyclohexylcarbodiimide or via an acid chloride.

As is apparent from the foregoing, compounds according to formula (VI), are useful for preparing compounds of formula (V), and constitute a part of this invention.

Scheme 3 illustrates some of the representative methods for preparing 2,3,4,5-tetrahydro-7-(4,4'-bipiperidinylcarbonyl)-3-oxo-4-methyl-1H-1,4-benzodiazepine-2-acetic acid.

Scheme 3


R = R¹ = OMe
R = R¹ = OH
R = OH, R¹ = H
a
b
R = R¹ = OMe 1
R = R¹ = OH 21
R = OH, R¹ = H 31
c
22 or 32
g
R = R¹ = OMe 2
R = R¹ = OH 22
R = OH, R¹ = H 32
R¹ = OH 23
R¹ = H 33
d
h
3
R¹ = OH 5, 24
R¹ = H 34
e
f
i
4
R¹ = OH
R¹ = H

(a) $MeNH_2$ (8.03M solution in EtOH), toluene (b) 10% Pd-C, EtOH, H_2 (c) N-Cbz-aspartic acid β-methyl ester, DCC, optionally HOBT; (d) ammonium cerium(IV) nitrate, MeCN, H_2O; (e) H_2, 10% Pd-C, ethanol; (f) potassium nitrosodisulfonate chloroform, acetic acid, HCl; (g) H_2, 10% Pd-C, ethanol; (h) potassium nitrosodisulfonate chloroform, acetic acid, HCl; (i) H_2, 10% Pd-C, ethanol, H_3P0_4

The meaning of any substituent at any one occurrence in formulas (I)-(VI) or any subformula thereof is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

Abbreviations and symbols commonly used in the chemical arts are used herein to describe the compounds, reactions and reagents of this invention.

Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, Boc refers to the t-butyloxycarbonyl radical, Ph refers to the phenyl radical, CBZ or Z refers to the benzyloxycarbonyl radical, Bn refers to the benzyl radical, Me refers to methyl, Et refers to ethyl, and Ac refers to acetyl.

Certain reagents are abbreviated herein. DCC refers to dicyclohexylcarbodiimide, DMAP refers to dimethylaminopyridine, DIEA refers to diisopropylethylamine. THF refers to tetrahydrofuran, DMF refers to dimethyl formamide, Pd-C refers to a palladium on carbon catalyst, TEA refers to triethylamine, TFA refers to trifluoroacetic acid.

C_{1-4}alkyl as applied herein is meant to include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl. C_{1-6}alkyl additionally includes pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. Any C_{1-4}alkyl or C_{1-6}alkyl group may be optionally substituted by halo, -OR', SR', -CN, -NR'R', $-NO_2$, $-CF_3$, $CF_3S(O)_r$-, $-CO_2R'$, $-CONR'_2$, C_{3-6}cycloalkyl, or Ar, unless otherwise indicated, where R' is H or C_{1-4}alkyl. A substituent on a C_{1-6} alkyl may be on any carbon atom which results in a stable structure, and is available by conventional synthetic techniques.

Ar, or aryl, as applied herein, means phenyl or naphthyl, or phenyl or naphthyl substituted by one to three moieties. In particular, such moieties may be C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, trifluoromethyl, OH, F, Cl, Br or I.

The reactive functional groups of each synthetic fragment are suitably protected as known in the art. Suitable protective groups are disclosed in Greene, PROTECTIVE GROUPS IN ORGANIC CHEMISTRY, John Wiley and Sons, New York, 1981. For example, the Boc, Cbz, phthaloyl or Fmoc group may be used for protection of an amino (or the nitrogen of a piperidinyl). The Boc or Cbz group is

generally preferred for protection of an amino group, such as on the basic nitrogen of a 4,4'-bipiperidinyl group. The term the basic nitrogen of the 4,4'-bipiperidinyl group, as used herein, indicates the nitrogen which is not attached to the benzodiazepine nucleus via a carbonyl group.

A methyl, ethyl, t-Bu, cHex, benzyl, substituted benzyl, (pivaloyl)methyl or (2-methyl-2-methoxypropanoyl)methyl ester may be used for the protection of the carboxyl group. A suitably substituted carbobenzyloxy group or benzyl group may be also be used for the hydroxyl group or amino group. Suitable substitution of the carbobenzyloxy or benzyl protecting groups is ortho and/or para substitution with chloro, bromo, nitro, methoxy or methyl, and is used to modify the reactivity of the protective group. C_{1-6}alkoxy, phenyl and benzyl are conventional carboxy protecting groups.

Methods for removal of the a carboxy or amino protecting group are well known in the art. For example, an alkyl or cycloalkyl ester may be removed by basic hydrolysis, for instance an alkali metal hydroxide, such as sodium, potassium or lithium hydroxide in a suitable solvent, such as aqueous alcohol. A benzyl ester is typically removed by hydrogenation over a palladium catalyst. A basic nitrogen protected by a t-butyloxycarbonyl group, or a t-butyl ester, is typically removed by acid treatment, such as by trifluoroacetic acid or hydrochloric acid, optionally diluted with a solvent, such as methylene chloride and/or dioxane. The benzyloxycarbonyl group is generally removed by hydrogenation over a palladium catalyst. A trifluoroacetyl group is typically removed by basic hydrolysis, such as by treatment with an alkali metal hydroxide in a suitable solvent. One useful synthetic method for protecting the basic nitrogen of a piperidinyl group is to carry the group through a synthesis as a pyridinyl group, which may be reduced with a platinum or palladium catalyst toward the end of the synthesis to remove the protecting group.

The simple starting materials for preparing the compounds of this invention are commercially available or prepared by routine methods well known in the art.

The intermediate compounds of this invention are useful as intermediates in the preparation of pharmaceutically active compounds, in particular compounds which have fibrinogen and vitronectin antagonist properties.

General

Nuclear magnetic resonance spectra were recorded at 270 MHz. $CDCl_3$ is deuteriochloroform, DMSO-d_6 is hexadeuteriodimethylsulfoxide, and CD_3OD is tetradeuteriomethanol. Chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane. Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz. HRMS indicates high resolution mass spectroscopy.

EXAMPLES

Example 1

Preparation of 2,3,4,5-tetrahydro-7-(*N*-CBZ-4,4'-bipiperidinylcarbonyl)-3-oxo-4-methyl-2-methoxycarbonylethylidenyl)-1H-1,4-benzodiazepine (9)

a) N-(2,5-dimethoxybenzylidine) methylamine.

To a solution of 2,5-dimethoxybenzaldehyde (20.00g, 0.12 mol) in toluene (100 ml) was added methylamine (22.5 ml of an 8.03M solution in ethanol, 0.18 mol) at room temperature. The solution became cloudy within 10 min. due to the condensation of water. The reaction had gone to completion within 30 min. according to GC analysis and the solvent was then removed in vacuo to give the required product; (21.17g, 98%) as a yellow oil. δH ($CDCl_3$, 270 MHz) 3.50 (3H, s), 3.80 (3H, s), 3.85 (3H, s), 6.80 (1H, m), 7.00 (1H, m), 7.50 (1H, m) and 8.70 (1H, s).

b) methyl (2,5-dimethoxybenzyl) amine (1)

A solution of *N*-(2,5-dimethoxybenzylidine) methylamine (21.17g, 0.12 mol) in ethanol (200 ml) was hydrogenated over 10% palladium on charcoal (water content 50%, 4.0g). The reaction had gone to completion within 2h according to GC analysis. The catalyst was filtered off and the filtrate was concentrated to dryness. The title compound was thus obtained as a yellow oil (18.00g, 85%); δH ($CDCl_3$, 270 MHz) 1.70 (1H, s br), 2.45 (3H, s), 3.70 (2H, s), 3.75 (3H, s) 3.80 (3H, s), 6.70 - 6.85 (3H, m).

c) (3*S*)-methyl 3-benzyloxycarbonylamino-4-(*N*-methyl-*N*-2,5-dimethoxybenzylcarbamoyl) butanoate (**2**)

To a solution of methyl (2,5-dimethoxybenzyl) amine (10.00g, 55.2mmol) and N-CBZ aspartic acid β-methyl ester (17.10g, 60.9mmol) in ethyl acetate (100 ml) was added dicyclohexylcarbo diimide (12.50g, 60.7mmol) at room temperature. A thick precipitate formed within 15 min. and after 1h the reaction mixture was filtered. The filtrate was concentrated to dryness to afford the crude required product as a thick oil and as a mixture of rotamers (30.73g, 100%) δH ($CDCl_3$, 270 MHz) 2.60 - 2.85 (2H, m), 2.90 (1.5H, s), 3.10 (1.5H, s), 3.65 (2H, s), 3.70 (3H, s), 3.80 (3H, s), 4.50 - 4.75 (1H, m), 5.05 (1H, d), 5.10 (1H, s), 4.70 (0.5H, d), 5.80 (0.5H, d), 6.70 - 6.80 (3H, m) and 7.25 - 7.40 (5H, m).

d) (3*S*)-methyl 3-benzyloxycarbonylamino-4-(*N*-methyl-*N*-(1,4-benzoquinonylmethyl) carbamoyl) butanoate (**3**)

To a solution of (3*S*)-methyl 3-benzyloxycarbonylamino-4-(*N*-methyl-*N*-2,5-dimethoxybenzylcarbamoyl) butanoate (**3**) (47.0g, 0.106mol) in acetonitrile (2.35L) was added cerium IV ammonium nitrate (145.5g, 0.265mol) in water (454 ml) at –14°C -10°C. The reaction mixture became dark brown-orange immediately and the colour became lighter over 1h. The temperature was allowed to rise to 5 - 10°C over 2h. and then to 12 - 15°C over 90 min. The solvent was then removed in vacuo and the residue was dissolved in dichloromethane (500 ml) and was washed with water. The aqueous layer was back extracted with dichloromethane (500 ml). The combined organic extracts were dried (Mg SO_4) and concentrated to dryness. The residue was chromatographed on silica gel using ethyl acetate as eluant. Hence the title compound was obtained as a viscous yellow oil (44.5g, 100%); δH ($CDCl_3$, 270 MHz) 2.60 – 3.00 (2H, m), 3.25 (3H, s), 3.70 (3H, s), 3.85 (1H, m), 4.40 (2H, ABq), 5.10 (2H, m), 5.60 (1H, d br), 6.55 (1H, m), 6.75 (2H, m) and 7.40 (5H, m).

e) (3*S*)-methyl 3-amino-4-(*N*-methyl-*N*-(2,5-dihydroxybenzyl) carbamoyl) butanoate (**4**)

A solution of (3*S*)-methyl 3-benzyloxycarbonylamino-4-(*N*-methyl-*N*-(1,4-benzoquinonylmethyl) carbamoyl)butanoate (44.5g, 0.100mol) in ethanol (1.50L) was hydrogenated over 10% palladium on charcoal (16.0g) at room temperature under one atmosphere of hydrogen for 16h. The catalyst was filtered off after this time and the filtrate was concentrated to dryness. (The crude product was not characterised but was used directly in the next step). δH (d-6 DMSO, 270 MHz

40°C) 2.40 (1H, dd), 2.70 (1H, dd), 2.90 (1.5H, s), 3.05 (1.5H, s), 3.30 (2H, s br), 3.60 (3H, s), 4.35 (1H, ABq), 4.50 (1H, ABq), 6.45 (2H, m) and 6.60 (1H, m).

f) 2,3,4,5-tetrahydro-7-hydroxy-3-oxo-4-methyl-2-(methoxycarbonylethylidenyl)-1H-1,4-benzodiazepine (**5**)

To a solution of (3*S*)-methyl 3-amino-4-(*N*-methyl-*N*-(2,5-dihydroxybenzyl) carbamoyl) butanoate (**4**) (30.30g, 0.107mmol) in water (2.08L) and acetic acid (233 ml) and chloroform (5.0L) was added hydrochloric acid (9.7 ml of an 11.0M aqueous solution, 0.107mmol) followed by Fremy's salt (63.4g, 0.237mol) in water (3.0L) at room temperature. The reaction mixture was stirred for 3h after which time the aqueous layer was separated. The chloroform layer was washed with water (1.0L) and was then concentrated to dryness. The resultant dark foamy residue was chromatographed on silica gel using ethyl acetate:hexane - 3:1 as eluant. Hence the title compound was obtained as white solid (7.29g, 26%). δH ($CDCl_3$, 270 MHz) 3.00 (3H, s), 3.75 (3H, s), 4.25 (2H, s br), 5.40 (1H, s), 5.80 (1H, s), 6.70 - 6.80 2H, m), 6.85 (1H, d) and 10.50 (1H, s). High Resolution Mass Spectrum (HRMS): Found M^+H 263.1016. $C_{13}H_{15}N_2O_4$ reqires 263.1032.

g) 2,3,4,5-tetrahydro-7-(trifluoromethanesulfonyloxy-3-oxo-4-methyl-2-methoxycarbonylethylidenyl)-1*H*-1,4-benzodiazepine (**6**)

To a solution of 2,3,4,5-tetrahydro-7-hydroxy-3-oxo-4-methyl-2-(methoxycarbonylethylidenyl)-1H-1,4-benzodiazepine (**5**) (1.00g, 3.82mmol) in pyridine (3.0 ml) was added trifluoromethanesulfonic anhydride (7.06 µl, 4.21mmol) at 0°C. The reaction mixture was stirred for 90 min. after which time it was diluted with ether (100 ml) and washed with water (250 ml). The aqueous layer was extracted with further ether (ca 100 ml) and the combined organic layers were dried ($MgSO_4$) and concentrated to dryness. The residue was chromatographed on silica gel using ethyl acetate:hexane - 2:3 as eluant. Hence the title compound was obtained as a white solid (1.10g, 73%) m/z 395 $[M+H]^+$, 363 $[M - MeOH+H]^+$, 335 $[M - HCO_2Me+H]^+$; δH ($CDCl_3$, 400 MHz) 3.10 (3H, s), 3.75 (3H, s), 4.30 (2H, s br), 5.50 (1H, s), 7.10 (1H, d), 7.15 (1H, d), 7.20 (1H, dd) and 10.70 (1H, s); HRMS: Found 394.0431. $C_{14}H_{13}F_3N_2O_6S$ requires 394.0446.

h) 2,3,4,5-tetrahydro-7-(*N*-CBZ-4,4'-bipiperidinylcarbonyl)-3-oxo-4-methyl-2-methoxycarbonylethylidenyl)-1H-1,4-benzodiazepine (7)

A 50 ml 3-necked flask containing a mixture of 2,3,4,5-tetrahydro-7-(trifluoromethanesulfonyloxy-3-oxo-4-methyl-2-methoxycarbonylethylidenyl)-1*H*-1,4-benzodiazepine (6) (0.27g, 0.68mmol), diisopropylethylamine (1.4 ml, 8.05mmol), *N*-CBZ-4,4'-bipiperidine hydrochloride (298 mg, 0.88mmol), palladium II chloride bistriphenylphosphine (10 mg, 0.014mmol) and water (30µl, 1.66mmol) in *N*-methylpyrrolidinone (2.2 ml) was evacuated and filled with carbon monoxide gas several times. The reaction mixture was then heated to 90 - 95°C under an atmosphere of carbon monoxide with vigorous stirring. After 5h palladium (0) tetrakistriphenylphosphine (100mg) was added and the carbonylation was continued. The reaction had gone to completion according to HPLC analysis after 16h. A solution assay of the reaction mixture against a reference standard indicated the yield to be 181mg, 46%. The reaction mixture was diluted with dichloromethane (30 ml) and was filtered. The filtrate was washed with water (2 x 30 ml) and was then concentrated to dryness in vacuo. The residue was chromatographed on silica gel using ethyl acetate as eluant to give the title compound as a pale yellow foam (144mg, 37%). This was triturated with ether (ca 4 ml) to give a purified sample as a white powder. m/z 575 $[M+H]^+$; δH ($CDCl_3$, 400 MHz) 1.10 - 1.45 (6H, m), 1.60 - 1.85 (4H, m), 2.75 (4H, m), 3.15 (3H, s), 3.75 (3H, s), 3.85 (1H, s v br), 4.15 - 4.30 (4H, m), 4.70 (1H, s br), 5.15 (2H, s), 5.45 (1H, s), 7.00 (1H, d), 7.30 - 7.40 (7H, m) and 10.70 (1H, s).

i) methyl 2,3,4,5-tetrahydro-7-(4,4'-bipiperidinylcarbonyl)-3-oxo-4-methyl-1H-1,4-benzodiazepine-2-acetate (8)

A suspension of 2,3,4,5-tetrahydro-7-(*N*-CBZ-4,4'-bipiperidinylcarbonyl)-3-oxo-4-methyl-2-methoxycarbonylethylidenyl)-1H-1,4-benzodiazepine (7) (375 mg, 0.653mmol) in methanol (20 ml) and water (10 ml) was acidified to pH 2.5 with a 26% aqueous solution of phosphoric acid. The resultant mixture was hydrogenated over 10% palladium on charcoal (Johnson Matthey type 87L, 375 mg) at 60 psi in a Parr Shaker at room temperature. The reaction had gone to completion within 2h according to HPLC analysis. The catalyst was filtered off and the filtrate was concentrated in vacuo to ca 5 ml. Water (10 ml) was added and the pH was then adjusted to 10 with a 35% aqueous solution of ammonia. A white precipitate formed and the suspension was cooled to 5°C for 16h. The precipitate was then filtered off

and dried in the open atmosphere to give the title compound as a white powder (257mg, 89%).

j) 2,3,4,5-tetrahydro-7-(4,4'-bipiperidinylcarbonyl)-3-oxo-4-methyl-1H-1,4-benzodiazepine-2-acetic acid (**9**)

The compound of Example 1(i) (0.26 mmol) was dissovled in methanol (9 ml), and 1.0 N sodium hydroxide (0.81 ml, 0.81 mmol) was added. The solution was stirred overnight at room temperature, and concentrated. The residue was dissolved in water/acetonitrile (3 ml), cooled to 0°C, acidified with HCl, and concentrated to yield the title compound.

Example 2

Preparation of 2,3,4,5-tetrahydro-7-(4,4'-bipiperidinylcarbonyl)-3-oxo-4-methyl-1H-1,4-benzodiazepine-2-acetic acid (12)

a) N-(2,5-hydroxybenzylidine) methylamine

Using the procedure of Example 1(a), except substituting 2,5-dihydroxy-benzaldehyde for 2,5-dimethoxy-benzaldehyde, the title compound was prepared. δH ($CDCl_3$, 270 MHz), 3.50 (3H,S), 6.75 (1H,m), 6.85 (2H,m) and 8.25 (1H,s)

b) N-methyl, N-(2,5-dihydroxybenzyl) amine (**21**)

Using the procedure of Example 1(b), except substituting the compound of Example 2(a) for the compound of Example 1(a), the title compound was prepared. δH ($CDCl_3$, 270 MHz) 2.25 (3H,S), 3.60 (2H,s) and 6.50 (3H,m).

c) (3*S*)-methyl 3-benzyloxycarbonylamino-4-(*N*-methyl-*N*-2,5-dihydroxybenzylcarbamoyl) butanoate (**22**)

Using the procedure of Example 1(c), except substituting the compound of Example 2(b), and chromatographing the crude product over silica gel using ethyl acetate:hexane – 1:1 – 1:0 as eluent, the title compound was prepared (46%). δH (CDCl, 270 MHz) 2.65 (1H,dd), 2.80 (1H,dd) 2.95 (3H,s), 3.60 (3H,s), 4.35 (2H, ABQ), 5.05 (2H,m), 5.80 (1H,d), 6.65 (1H,s), 6.75 (2H,m), 7.25 - 7.50 (5H,m) and 8.60 (2H,s(br)).

e) (3*S*)-methyl 3-amino-4-(*N*-methyl-*N*-(2,5-dihydroxybenzyl) carbamoyl) butanoate (**23**)

A solution of **22** (7.82g, 18.80 mmol) in absolute ethanol 107ml was hydrogenated over 10% palladium on charcoal (0.78g) for 20h. The catalyst was filtered off and the filtrate was concentrated to dryness. The residue was chromatographed on silica gel using ethyl acetate : dichloromethane : methanol - 4:4:2 as eluant. The title compound was obtained as a colourless foam (3.6g, 65%).

f) 2,3,4,5-tetrahydro-7-hydroxy-3-oxo-4-methyl-2-(methoxycarbonyl ethylidenyl)-1H-1,4-benzodiazepine (**24**)

Using the procedure of Example 1(f), except subtituting the compound of Example 2(e) for the compound of Example 1(e), the title compound was prepared.

g) 2,3,4,5-tetrahydro-7-(4,4'-bipiperidinylcarbonyl)-3-oxo-4-methyl-1H-1,4-benzodiazepine-2-acetic acid (**9**)

Using the compound of Example 2(f) and following the procedures of Examples 1(d) - 1(j), the title compound is prepared.

Example 3

Preparation of 2,3,4,5-tetrahydro-7-(4,4'-bipiperidinylcarbonyl)-3-oxo-4-methyl-1H-1,4-benzodiazepine-2-acetic acid

a) N-(2-hydroxybenzylidine) methylamine

Using the procedure of Example 1(a), except substituting 2-hydroxy-benzaldehyde for 2,5-dimethoxy-benzaldehyde, the title compound was prepared. δH ($CDCl_3$, 270MHz) 6.80 (1H,t), 7.00 (1H,s), 7.20-7.30 (2H,m) and 8.40 (1H,s).

b) N-methyl, N-(2-hydroxybenzyl) amine (**31**)

Using the procedure of Example 1(b), except substituting the compound of Example 3(a) for the compound of Example 1(a), the title compound was prepared. δH ($CDCl_3$, 270MHz) 2.50 (3H,s), 4.00 (2H,s) 6.75 (1H,t),6.80 (1H,d), 7.00 (1H,d) and 7.20 (1H,t).

c) (3*S*)-methyl 3-benzyloxycarbonylamino-4-(*N*-methyl-2-hydroxybenzylcarbamoyl) butanoate (**32**)

Using the procedure of Example 1(c), except substituting the compound of Example 3(b) for the compound of Example 1(b) and adding HOBT (1.1 equiv), and chromatographing the crude product using ethyl acetate:hexane – 4:6 – 1:0 as eluent, the title compound was prepared (82%). δH ($CDCl_3$, 270MHz) 2.65 (1H,dd), 2.80 (1H,dd), 3.20 (3H,s), 3.60 (3H,s), 4.40 (2H,ABQ), 5.10 (2H,m),5.70 (1H,d), 6.80 (1H,t), 6.90 (1H,d), 7.15 (1H,dd), 7.25 (1H,dt) and 9.05 (1H,s).

d) (3*S*)-methyl 3-amino-4-(*N*-methyl-*N*-(2-hydroxybenzyl) carbamoyl) butanoate (**33**)

A solution of 32 (11.26g 28.15mmol) in absolute ethanol (78ml) was hydrogenated over 3% palladium on charcoal (2.62g) at room temperature for 2h. The catalyst was filtered off and the filtrate was concentrated to dryness. The residue was chromatographed on silica gel using ethyl acetate: chloroform: methanol – 9:9:2 as eluant. The title compound was obtained as acolourless foam (6.90g, 92%). δH ($CDCl_3$, 270MHz) 2.55 (1H,dd), 2.70 (1H,dd), 3.20 (3H,s), 3.65 (3H,s), 4.15 (1H,t), 4.50 (2H,ABQ), 6.80 (1H,t) 6.95 (1H,d), 7.15 (1H,d) and 7.25 (1H,t). $[M+H\}^+$ 267

Using the procedure of Example 1(f), except substituting the compound of Example 3(e), the title compound is prepared.

f) methyl 2,3,4,5-tetrahydro-3-oxo-4-methyl-1H-1,4-benzodiazepine-2-acetate

Following the procedure of Example 4, except substuting the compound of Example 3(e), the title compound is prepared.

g) methyl 2,3,4,5-tetrahydro-7-(4,4'-bipiperidinylcarbonyl)-3-oxo-4-methyl-1H-1,4-benzodiazepine-2-acetate (**9**)

Following the procedures set forth in WO 97/24336 (PCT/IB96/01502), the title compound is prepared.

Example 4

Preparation of methyl 2,3,4,5-tetrahydro-7-hydroxy-3-oxo-4-methyl-1H-1,4-benzodiazepine-2-acetate (**10**)

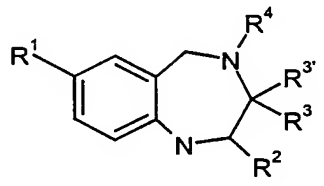
A solution of the compound of Example 1(f) (1.73g, 6.6mmol) in absolute ethanol (173ml) was hydrogenated over 10% palladium on charcoal (1.73g) for 16h.

at room temperature. The catalyst was then filtered off and the filtrate was concentrated to dryness. The residue was slurried in dichloromethane; ether - 1:1 and the product was then filtered off as a white solid (800mg, 46%). δH (DMSO, 270MHz) 2.60(1h, dd), 2.80(1H, dd), 2.90 (3H, s), 3.60(3H,s), 3.75(1H, d), 4.80(1H,m), 5.10(1H,d), 5.35(1H, d), 6.40(3H, m) and 8.55(1H, s).

The above description fully discloses how to make and use the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprises the state of the art and are incorporated herein by reference as though fully set forth.

Claims:

1. A process for preparing a compound of the formula (I):



(I)

wherein,

R^1 is H, OH, Br, I, NR^5R^6, CO_2R^7, CF_3SO_3, C_{1-4}alkoxy, or (4,4'-bipiperidinyl)carbonyl;

R^2 is alkyl, optionally substituted by CO_2R^7 or $CONR^5R^6$;

R^3 and $R^{3'}$ are independently H, Ar or C_{1-6}alkyl optionally substituted by OH, NO_2, NH_2, NR^5R^6, halogen, CO_2R^7, $CONR^5R^6$or Ar, or together R^3 and $R^{3'}$ are =O;

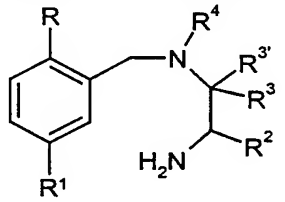
R^4 is H or C_{1-4} alkyl, optionally substituted by OH, NO_2, NH_2, NR^5R^6, halogen, CO_2R^7, $CONR^5R^6$, or Ar;

R^5 and R^6 are independently H, Ar, C_{1-6}alkyl, HCO, C_{1-6}alkyl-CO, Ar-CO, C_{1-6}alkyl-SO_2, or Ar-SO_2; and

R^7 is a carboxylic acid protecting group,

which comprises

reacting a compound of the formula (II) with an oxidizing agent,



(II)

wherein

R is OH or C_{1-4}alkoxy, and R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined above, and,

thereafter, treating with a reducing agent.

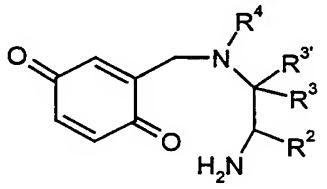
2. A process according to claim 1 wherein R^2 is $CH_2CO_2R^7$, and together R^3 and $R^{3'}$ are =O.

3. A process according to claim 1 wherein R^1 is H, OH or C_{1-4}alkoxy.

4. A process according to claim 1 wherein the oxidizing agent is potassium ferricyanide or potassium nitrosodisulfonate.

5. A process according to claim 1 wherein the reducing agent is hydrogen in the presence of a palladium or platinum on carbon catalyst.

6. A compound of formula (III):



(III)

wherein,

R^2 is alkyl, optionally substituted by CO_2R^7 or $CONR^5R^6$;

R^3 and $R^{3'}$ are independently H, Ar or C_{1-6}alkyl optionally substituted by OH, NO_2, NH_2, NR^5R^6, halogen, CO_2R^7, $CONR^5R^6$or Ar, or together R^3 and $R^{3'}$ are =O;

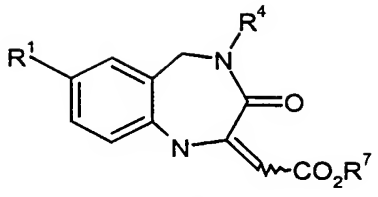
R^4 is H or C_{1-4} alkyl, optionally substituted by OH, NO_2, NH_2, NR^5R^6, halogen, CO_2R^7, $CONR^5R^6$, or Ar;

R^5 and R^6 are independently H, Ar, C_{1-6}alkyl, HCO, C_{1-6}alkyl-CO, Ar-CO, C_{1-6}alkyl-SO_2, or Ar-SO_2; and

R^7 is a carboxylic acid protecting group,

7. A compound according to claim 6 which is (3*S*)-methyl 3-amino-4-(*N*-methyl-*N*-(1,4-benzoquinonylmethyl) carbamoyl) butanoate.

8. A method for preparing 2,3,4,5-tetrahydro-7-(4,4'-bipiperidinylcarbonyl)-3-oxo-4-methyl-1H-1,4-benzodiazepine-2-acetic acid
comprising, in any order, reacting a compound of formula (V):



(V)

wherein

R^1 is H, OH, Br, I, C_{1-4}alkoxy, CO_2R^7, CF_3SO_2, or (4,4'-bipiperidinyl)carbonyl, optionally protected on one nitrogen;

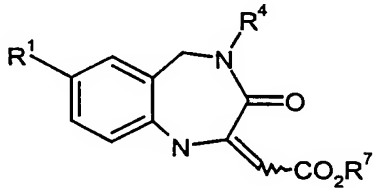
R^4 is methyl, and

R^7 is a carboxy protecting group;

with a reducing agent, and, if necessary, converting R^1 to (4,4'-bipiperidinyl)carbonyl; and

if necessary, removing any protecting groups.

9. A compound of the formula:



(V)

wherein

R^1 is H, OH, I, Br, C_{1-4}alkoxy, CO_2R^7, CF_3SO_2, or (4,4'-bipiperidinyl)carbonyl optionally protected on the basic nitrogen;

R^4 is methyl, and

R^7 is a carboxy protecting group.

10. A compound according to claim 8, which is:

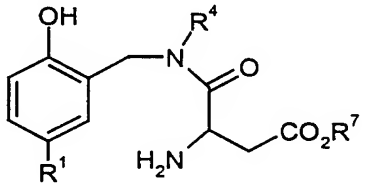
2,3,4,5-tetrahydro-3-oxo-4-methyl-2-(methoxycarbonyl ethylidenyl)-1H-1,4-benzodiazepine;

2,3,4,5-tetrahydro-7-hydroxy-3-oxo-4-methyl-2-(methoxycarbonylethylidenyl)-1H-1,4-benzodiazepine;

2,3,4,5-tetrahydro-7-(trifluoromethanesulfonyloxy-3-oxo-4-methyl-2-methoxycarbonylethylidenyl)-1*H*-1,4-benzodiazepine; or

2,3,4,5-tetrahydro-7-(*N*-CBZ-4,4'-bipiperidinylcarbonyl)-3-oxo-4-methyl-2-methoxycarbonylethylidenyl)-1H-1,4-benzodiazepine.

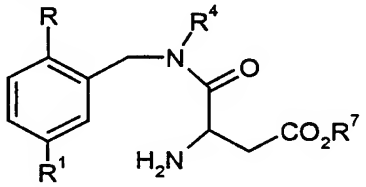
11. A method for preparing 2,3,4,5-tetrahydro-7-(4,4'-bipiperidinylcarbonyl)-3-oxo-4-methyl-1H-1,4-benzodiazepine-2-acetic acid, comprising reacting a compound of the formula:



(VI)

wherein R^1 is H, OH, Br, I, C_{1-4}alkoxy, CO_2R^7, CF_3SO_3, or (4,4'-bipiperidinyl)carbonyl, optionally protected on one nitrogen;
R^4 is methyl, and
R^7 is a carboxy protecting group;
with an oxidizing agent, and, in any order, treating with a reducing agent; and, if necessary, converting R^1 to (4,4'-bipiperidinyl)carbonyl; and removing any protecting groups.

12. A compound of the formula:



(II)

wherein
R is OH or C_{1-4}alkoxy;
R^1 is H, OH, Br, I, C_{1-4}alkoxy,CO_2R^7, CF_3SO_3, or (4,4'-bipiperidinyl)carbonyl, optionally protected on the basic nitrogen;;
R^4 is methyl, and
R^7 is a carboxy protecting group.

13. A compound according to claim 11, which is:
(3*S*)-methyl 3-amino-4-(*N*-methyl-*N*-(2,5-dihydroxybenzyl) carbamoyl) butanoate;
or
(3*S*)-methyl 3-amino-4-(*N*-methyl-*N*-(2-hydroxybenzyl) carbamoyl) butanoate.

INTERNATIONAL SEARCH REPORT

ternatic Application No
PCT/EP 00/03260

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D243/14 C07C225/12 C07C237/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	J. F. HAYES: "An Alternative Synthesis of a Potent GPIIb/IIIa Receptor Antagonist" SYNLETT, no. S1, 1999, pages 865-6, XP000915438 schemes 2, 3; pages 865, right-hand column to page 866, left-hand column --- -/--	1-3,5,6, 8,9,11, 12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
14 July 2000	26/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

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INTERNATIONAL SEARCH REPORT

Ternatic Application No
PCT/EP 00/03260

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	J. M. SAMANEN ET AL.: "Potent, Selective, Orally Active 3-Oxo-1,4-benzodiazepine GPIIb/IIIa Integrin Antagonists" JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, no. 25, 6 December 1996 (1996-12-06), pages 4867-70, XP002142556 page 4869, scheme 1 ---	1,2,6,9, 11,12
A	WO 93 00095 A (SMITHKLINE BEECHAM CORP.) 7 January 1993 (1993-01-07) cited in the application page 21, scheme 2 ---	1,6,9,12
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A	R. M. KEENAN ET AL.: "Conformational Preferences in a Benzodiazepine Series of Potent Nonpeptide Fibrinogen Receptor Antagonists" JOURNAL OF MEDICINAL CHEMISTRY, vol. 42, no. 4, 25 February 1999 (1999-02-25), pages 545-59, XP002142557 tables 1,2 ---	9
A	WO 95 18619 A (SMITHKLINE BEECHAM CORP.) 13 July 1995 (1995-07-13) cited in the application abstract ---	9
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